Remarks

The Office Action mailed September 8, 2004, has been received and reviewed. The pending claims were claims 1-7, 9, 10, 15-32, 39, 42-48, 57 and 61-74, of which claims 42-47, 57, 61, and 64-67 were withdrawn and claims 8, 11-14, 40-41, 49-56, and 58-60 were canceled. Claims 1, 16, 18, 20-23, 39, and 63 are currently amended and new claims 75 - 80 have been added. Please cancel claims 26, 42-47, and 57 without prejudice. Support for the amendment to in vivo methods is found on page 16, line 4, while support for the new "ex vivo" claims 75 and 76 can be found, for example, on pages 15-16, lines 30-4. Support for new claim 77 can be found, for example, on page 13, lines 26-27. Support for new claim 78 can be found, for example, on page 12, lines 19-21, and support for new claims 79 and 80 can be found, for example, on page 12, lines 16-19, The currently pending claims are claims 1-7, 9, 10, 15-25, 27-32, 39, 48, and 61-80 while the claims currently under examination are claims 1-7, 9, 10, 15-25, 27-32, 39, 48, 62, 63, and 68-80. Reconsideration and withdrawal of the rejections are respectfully requested.

Applicant notes that the Office Action Summary mailed September 8, 2004 did not confirm receipt of the amended drawings. Amended Figure 13 was filed on April 28, 2003. Applicant respectfully requests that the Examiner indicate the status of the amendment to the drawings in the next official communication.

The 35 U.S.C. §132 Objection to the Introduction of New Matter

The Examiner objected under 35 U.S.C. §132 to the amendment filed April 28, 2003 for introducing new matter into the disclosure. Specifically, the Examiner argues that the added material is not supported by the original disclosure. Further, the Examiner states that the changes in the specification are not commensurate in scope with that of the affidavit, which referred to "rat ROS cells" rather than "rat cells", and that there is no factual evidence accompanying the affidavit under 37 CFR 1.132 to support the inventor's assertion that the error was inadvertent. Applicants respectfully traverse the objection.

Regarding the first half of the Examiner's objection, the original specification states on page 4, lines 21-22 that "[t]he vertebrate cell is preferably a fish cell, a murine cell, a bird cell or a human cell." The term "murine" is defined as "pertaining to or affecting mice or rats." Dorland's Illustrated Medical Dictionary, 29th edition, p. 1140 (2000). Later, the specification specifically refers to rats on p. 10, lines 22-23, stating "[e]xamples of vertebrates include fish and mammals, including cattle, goat, pig, sheep, hamster, mouse, rat, and human." Inclusion of the term "rat cells" into the specification rather than "rat ROS cells" does not constitute new matter, as it is supported by the generic term murine as well as specific mention of rats.

The Examiner also objected to the absence of factual evidence accompanying the supplemental declaration submitted under 37 CFR §1.132 containing the inventor's statement that the error in the specification as originally filed was inadvertent. Applicants do not believe that it is necessary to provide factual evidence that the error was inadvertent, as M.P.E.P. §716.01(c) indicates that evidence is only required for "evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Furthermore, as intent is a subjective, rather than objective element, the declaration of the inventor as to the inadvertency of the omission should suffice. If the Examiner maintains that evidence of intent is necessary, Applicants respectfully request that the Examiner provide the legal basis for this requirement.

In light of the arguments provided above, Applicants respectfully request that the objection under 35 U.S.C. 132 be withdrawn, as no new matter has been introduced.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 under 35 U.S.C. §112, first paragraph, alleging that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Examiner states that the specification, while

enabling for a method of attenuating the expression of specific disclosed target genes in zebrafish cells or embryos, attenuating the expression of the specific disclosed gene in avian neural crest tissue explant culture, and attenuating the expression of the specific disclosed gene in rat [formerly murine NIH/3T3] cell culture, does not reasonably provide enablement for attenuating the expression of any gene in any *in vivo* or *in vitro* vertebrate cell, or for attenuating the expression of any gene in any explant tissue culture or attenuating the expression of any gene in any cell type culture. This rejection is respectfully traversed. Claim 26 has been canceled, rendering the rejection moot with respect to that claim.

The Examiner has based the rejection for asserted lack of enablement on the factors enumerated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). However, while the Examiner has listed the factors enumerated in *In re Wands*, (i.e., breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working example, and the quantity of experimentation needed to make the invention based on the content of the disclosure), the Examiner has focused almost exclusively on two of the factors; namely, the breadth of the claims and the level of predictability in the art. *In re Wands*, however, as well as the recent case *In re Curtis*, 354 F.3d 1347 (Fed. Cir. 2004) state that it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the factors while ignoring one or more of the others. This is further reinforced by the Examiner's Training Manual, which states that "The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole." As the Examiner has not properly applied a full analysis of the Wands factors, Applicant respectfully submits that the rejection of the claims for lack of enablement under 35 U.S.C. § 112, first paragraph, should be withdrawn.

The Examiner's first argument regarding the rejection under 35 U.S.C. §112 appears to involve the breadth of the claims. As the Examiner has here indicated that the specification is enabling for attenuating the expression of specific disclosed target genes in specific disclosed

species, the central issue is whether sufficient genes and species of vertebrate cells are provided by the specification to support the genus of all genes in vertebrate cells. The standard for such situations is set out in M.P.E.P. § 2164.02, where it states that "For a claimed genus, representative examples and a description of how to make and use the genus as a whole should be sufficient if a person skilled in the art would expect the claimed genus could be used in that manner without undue experimentation." It is submitted that Applicants have made an adequate showing of enablement in the specification for the claimed genus. Applicants have demonstrated, by working, representative examples, the specific attenuation of gene expression using double-stranded RNA (dsRNA) in the following diverse systems:

Cell/Organism/Tissue	Targeted Gene	Gene Function/Phenotype
zebrafish embryo	GFP	exogenous reporter gene (plasmid based)
zebrafish embryo	T gene	endogenous gene associated with midline development: *no tail* (*ntl*) phenotype
zebrafish embryo	Pax6.1	endogenous gene associated with head and eye development
zebrafish embryo	Nkx 2-7	endogenous gene associated with heart morphology and functioning
zebrafish embryo	T gene Pax6.1	see above (two genes targeted)
chick neural crest tissue	HirA	endogenous gene associated with persistent truncus arteriosus
murine NIH/3T3 cells	GFP	exogenous reporter gene (plasmid based)

Applicants direct the Examiner to M.P.E.P. § 2164.02 on Working Examples and a Claimed Genus, where it states that:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art ... would expect the calimed genus could be used in that manner without undue experimentation. Proof of

> enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

It can be seen that Applicants have shown successful gene silencing using dsRNA in a wide range of systems targeting a wide range of genes, and have provided numerous working examples. Vertebrate cells as diverse as fish cells, mammalian cells and avian cells were silenced. And these are merely the vertebrate organisms for which examples are provided; the specification further describes the target gene as being derived from any organism, with numerous examples of additional species being provided. In addition to disclosing a large number of species, Applicants have used an organism that is designed to be representative of the genus. The zebrafish is not merely a fish but is rather a model organism for studies of vertebrate organisms. In fact, experts have promoted the use of the zebrafish as a model for human biology. See "The Zebrafish Model Organism Database" available at http://zfin.org/zf_info/dbase/db.html. Given the Examples provided, as well as the rest of the support provided throughout the application, Applicants have satisfied the standard described above for enablement, and the rejection under 35 CFR § 112 on this ground should be withdrawn.

In addition to evaluating genes present in a number of different species, the phenotypes that were generated for each gene differed substantially from one another and, in addition, were specifically and predictably related to the gene that was targeted (specification at page 34, line 32, bridging to page 35, line 2). For example, functionally attenuating expression of the zebrafish T gene resulted in a reproducible phenotype that mirrored that found of the *ntl* mutant where the same gene was altered by an insertional mutation (specification at page 31, line 16-18). Injection of control dsRNA at the same concentrations, on the other hand, did not cause a detectable deviation from the wild-type expression levels or phenotype (specification at page 35, line 2-4). Furthermore, Applicants have shown that multiple genes can be targeted simultaneously (specification at, for example, page 35, lines 8-9), further evidencing the robustness of the method of the invention. Applicants have also shown that the timing and/or

amount of the dsRNA injected can predictably generate partial phenotypes of varying severity.

The Examiner further argues that sufficient guidance has not been provided regarding which genes should be targeted for methods of treating a disease or infection, as recited in claims 72 and 73. Applicant notes that such guidance is simply not pertinent to the method claimed, as the method is intended to allow the user to choose to suppress expression of a target gene of their choice. Applicant has not described a particular method of therapy directed at a particular gene, but instead has described a novel method of silencing genes that can be applied to silence a wide variety of genes. Selection of particular genes and determining their sequence is routine to those skilled in the art, and the claims are limited to methods in which dsRNA is supplied that is capable of hybridizing, under specific conditions, to the target gene selected.

The bulk of the Examiner's rejection under 35 U.S.C. § 112 revolves around arguing that the claims are not enabled due to the unpredictability involved in inhibiting expression of a target gene in vertebrates by RNA interference (RNAi). The Examiner then cites numerous examples of post-filing art to support the proposition that the claimed method is unpredictable. Applicants note, at the outset, that it is improper to use post-filing art to demonstrate a lack of enablement. This was made clear by the CCPA in *In re Hogan*, 559 F.2d 595, 194 USPQ 527 (CCPA 1977), in which the CCPA expressed concern that subsequently generated art could be used to attack pioneering patents and thus hinder early disclosure. There are only limited exceptions to this rule, such as the use of post-filing art to demonstrate that one of ordinary skill in the art would not have reasonably believed the prophetic teachings of a specification as of its filing date (In re Wright, 999 F.2d at 1562, 27 USPQ2d at 1513 (Fed. Cir. 1993)).

Moreover, Applicants note that there are large quantities of post-filing art that support predictability. Applicant directs the Examiner's attention to, for example, the work of McCaffrey et al., who have used double stranded RNA to specifically inhibitor luciferase expression in mice (McCaffrey et al., Nature, 418, 39 (2002), Rossi et al., who have shown that dsRNA can be delivered in vivo by conjugation to cholesterol (Rossi, J., Nature, 432, 155

(2004), the silencing of apolipoprotein B in mice by dsRNA (Soutschek et al., Nature 432, 173 (2004)), the lack of an interferon response to naked siRNA in animals (Heidel et al., Nature Biotechnology, 22(12), 1579 (2004)), and the use of RNAi to inhibit neurodegeneration in polyglutamine disease in mice (Caplen N., Nature Medicine, 10(8), 775 (2004)). In a review cited by the Examiner, Caplen states "RNAi appears to have many advantages over that of previous technologies developed for the downregulation of gene expression" (p. 581, second column) and that "RNAi is remarkably specific" (p. 577, bottom of second column) (Caplen, N., Expert. Opin. Biol. Ther., 3 (2003).

Notwithstanding the inappropriateness of their use to challenge enablement, Applicants feel compelled to offer counterpoints to some of the comments made by the Examiner regarding post-filing art. Fire (Trends in Genetics, v. 15, 358-363 (1999)), which was introduced by the Examiner as evidence of the unpredictability of gene attenuation, actually contradicts the Examiner's conclusion of unpredictability. In answering the question "Can any RNA be a target of PTGS (post-transcriptional gene silencing)" posed in the first column at page 360, Fire begins by noting that "*[i]n each system examined*, numerous mRNAs can be targets of dsRNA-triggered PTGS" (emphasis added). He further states that "sensitivity to dsRNA-triggered PTGS appears to be *the rule rather than an exception*" (emphasis added). It is only in considering the "exceptions" that Fire speculates that there might be some target RNAs that partially or fully resist PTGS, and that naturally stable RNAs are likely to be dramatically more affected, whereas RNAs that are rapidly synthesized and degraded might be less affected. Indeed, Applicants submit that the overall message of the Fire review article is that gene silencing in lower organisms is surprisingly predictable, although many mechanistic questions remain to be resolved (Fire at page 358, abstract and second column). The review by Fire thus supports, rather than challenges, enablement of the present claims.

The Examiner cites another reference by Fire et al. (Nature 391, 806-11 (1998)), this time a pre-filing date reference, for the proposition that introduction of dsRNA can result in a mosaic pattern of interference, or resistance to interference may be observed. Applicants submit that the

main observation of Fire et al. is that "[t]he phenotype produced by interference...was *extremely specific*. Progeny of injected animals exhibited behaviour that *precisely mimics* loss-of-function mutations..." (emphasis added) (Fire et al. at page 808, second column). Indeed, out of 19 dsRNA segments tested, the effects of all but one were limited to those expected from previously characterized null mutants, indicating remarkably reproducible specificity (Fire et al. at page 809, first column). The one exception was a protein with a highly conserved myosin-motor domain, and Applicants submit that one of ordinary skill in the art would suspect that dsRNA in that case would be expected to interfere with other related proteins.

Notably, observations of Fire et al. concerning mosaicism do not argue against specificity, and the fact that dsRNA segments corresponding to various intron and promoter sequences did not produce detectable interference still did not rule out interference at the level of the gene (Fire et al. at page 809, second column). The authors note that the use of dsRNA injection makes it possible to functionally analyze many interesting coding regions for which no specific function has been defined. They describe dsRNA-mediated interference as "potent" and "specific" (Fire et al. at page 810, first column). The additional observations that (1) a sequence shared between several closely related genes may interfere with several members of the gene family; (2) low level of expression may resist RNA-mediated interference for some or all genes and (3) a small number of cells will escape these effects do not render the technology unpredictable; they are more fairly categorized as relatively routine considerations in experimental design.

The Examiner provided additional argument and examples of post-filing art to support the asserted unpredictability of attenuating inhibition of a target gene in vertebrate cells by RNA interference in paragraphs 7 through 13. These address ancillary issues such as the degree of attenuation, toxicity, and the possible generation of an immune response. It is submitted that these concerns do not render the invention unpredictable *as claimed.* Claims to the present invention do not specify a degree of attenuation, but rather merely that expression *is* attenuated, which is defined in the specification merely as "partial or complete inhibition of gene function."

A similar statement can be made with regard to toxicity and immunogenicity, which are simply not pertinent to the invention as claimed.

Further regarding toxicity and a possible immune response; Applicants note that these types of issues have been raised under the "how to use" aspect of 35 U.S.C. §112 for pharmaceutical use in humans. The issue was address in *In re Krummel*, 292 F.2d 948, 130 U.S.P.Q. 215 (C.C.P.A 1961), where the court stated:

> "There is nothing in the patent statute ... which gives the Patent Office the right or the duty to require an applicant to prove that compounds or other materials which he is claiming ... are safe, effective, and reliable for use with humans."

This issue was further addressed in *In re Hartop*, 311 F.2d 249, 135 U.S.P.Q. 419 (C.C.P.A. 1962) in which that CCPA held that absolute safety was not required, stating:

> "Congress has recognized this problem and has clearly expressed its intent to give statutory authority and responsibility in this area to Federal agencies different than that given to the patent office."

As this is the standard applied for pharmaceutical use in humans, which one would expect to be the highest standard possible, Applicants in the present case should not be required to prove the absence of toxicity and possible immune responses when claims are directed to attenuation of gene expression in vertebrate cells. This is particularly true in light of the lack of terms regarding toxicity or immunogenicity in Applicant's claims.

The Examiner also expressed particular concern on the issue of nucleotide delivery in vertebrate organisms in paragraphs 14-27. For example, in paragraph 27, the Examiner states that "Methods of inhibiting gene expression using nucleic acids in vivo are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a loss of function phenotype."

Applicants respectfully point to page 14, line 29 to page 16, line 25, of the specification which provides numerous details on delivery of dsRNA. For example, the section on "Delivery of dsRNA to a cell" describes how to deliver dsRNA to an embryo, cell culture, and whole animals or plants. The specification also lists numerous methods, such as microinjection, particle bombardment, soaking the cell or organism in a solution containing the dsRNA, electroporation of cell membranes, etc. (see p. 14, lines 1-5). The dsRNA can also be delivered to a cell using a vector that encodes a dsRNA and causes the dsRNA to be transcribed within the cell (see p. 14, lines 21-27). Applicant further provides detailed examples of the use of microinjection in Example I and soaking in solution containing the dsRNA in Examples II and III. While cellular uptake was a concern early in the development of nucleotide-based treatment, researchers have come to understand that cells readily internalize nucleic acids and many such methods are well-established in the art.

The Examiner has also argued that delivery of interfering RNA is not enabled by the application, noting in paragraph 14 that "while prior art references teach administration to invertebrates using several broadly disclosed methods (such as microinjection into a body cavity of *C. elegans* and feeding *E. Coli* which express dsRNA to *C. elegans*), the prior art does not address administering dsRNA to vertebrates and thus does not teach successfully delivery..." Applicants respectfully disagree the Examiner's argument regarding delivery.

With regard to delivery, the claims recite "supplying the cell with a double stranded RNA" for attenuating gene expression. Thus, all that is required to enable claims of the invention with regard to the issue of delivery is that methods of supplying a cell with double stranded RNA are provided by the specification or known to those skilled in the art. Applicants submit that the present application readily meets this standard. The specification (p. 14, lines 9-20) recites numerous ways of supplying dsRNA to a particular organ or location within an organism, all of which are well known to those skilled in the art. Furthermore, the Examples demonstrate how to supply dsRNA to cells in cell culture (Example III), a pluripotent embryo cell with the consequent, predicted organismal change in phenotype (Example I), and tissue

explant (Example II). As the claims merely recite *supplying the vertebrate cell with dsRNA*, many of the traditional pharmacological concerns, such how the dsRNA will be metabolized, how it can be targeted to a particular location within an organism are simply not pertinent, as the dsRNA can be directly delivered to the site of interest by methods such as injection into a cavity. In the case of an expression vector encoding the dsRNA, there is ample teaching in the art relating to delivery of such vectors into vertebrate cells. See, for example, U.S. Patent No. 5,580,859, entitled "Delivery of exogenous DNA sequences in a mammal," which teaches direct injection of a "naked" DNA expression vector into a mammal.

The Examiner has provided numerous references describing technical difficulties encountered in delivering nucleotides, but the majority of these deal with antisense nucleotides, which are generally single stranded DNA, making them distinct from the double stranded RNA used for the present invention. Furthermore, antisense oligonucleotides actually work very well in a variety of in vivo settings. Local delivery (e.g., intra opthalmically, inhalation, topically, etc.) generally provides the best results. However, the literature contains many examples of systemic delivery of antisense that have worked very well, and the majority of clinical trials currently ongoing with antisense oligonucleotides utilize systemic (primarily intravenous) delivery methods. The use of double stranded RNA also distinguishes the present claims from many studies on siRNAs in which small, single strands of RNA were used. Furthermore, these reviews uniformly attest to the enormous progress made in the field of nucleotide delivery. For example, Wang et al. (Antisense and Nucleic Acid Drug Development, 13, 169 (2003)) state on page 169 that "With advances in oligonucleotide chemistry and progress made in formulation development, oligonucleotides are becoming widely acceptable drugs." The review by Wang et al. further describes how to specifically target oligonucleotides for the liver, and how to administer oligonucleotides by oral and colorectal administration, topical, and pulmonary delivery.

Applicant noted above that the Examiner has based the rejection for asserted lack of enablement on the factors enumerated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404

(Fed. Cir. 1988). Applicant further noted that the Examiner had only addressed a minority of the Wands factors, and that application of the factors required a balanced analysis of all of the factors listed. To help provide a balanced analysis, Applicants note that the level of one of ordinary skill in this area is quite high. Further, the Application contains numerous working examples using a wide variety of genes in vertebrate classes as diverse as fish, birds, and mammals that direct how to carry out the invention. The nature of the invention is further of a ground-breaking nature, and as such will inherently not have all of the features of a fully developed technology. And while the biological sciences are relatively unpredictable, sufficient guidance has been provided to carry out the invention within the breadth of the claims. Furthermore, commensurate with the unpredictability of the biological sciences is the expectation that even a fully developed therapeutic technique will not be completely predictable in its execution, and therefore such a standard should not be applied here.

Finally, with regard to enablement, Applicants note that the presumption is that an application is enabled, and that this is overcome only if the Examiner can show that undue experimentation is necessary to use the invention as claimed. Furthermore, the mere fact that experimentation may be involved, and even be complex, does not necessarily make the experimentation undue. Applicants do not believe undue experimentation would be necessary to practice the invention as claimed. It is well-established that some experimentation is often to be expected in unpredictable technologies, such as molecular biology. The question is whether the amount of experimentation needed to practice the invention, as claimed, is undue. This question is answered more readily if the method of the invention is broken down into separate steps. For the first step, to attenuate the expression of a target gene in a vertebrate cell, the nucleotide sequence of the gene can obtained either from a database or from routine procedures used to determine the sequence of a gene. RNA capable of hybridizing to the target gene is then synthesized, again using routine methods known to those skilled in the art. Finally, the dsRNA is supplied to a vertebrate cell through the delivery methods discussed above, which are again routine and known to those skilled in the art. It is thus respectfully submitted that Applicants

have demonstrated that the introduction of dsRNA into vertebrate cells in accordance with the method of the invention results in the attenuation of expression of target genes, without undue experimentation. It is accordingly submitted that the invention of claims 1-7, 9, 10, 15-25, 27-32, 39, 42-48, 57 and 61-74 is adequately enabled. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is accordingly requested.

The Examiner further rejected claims 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 as failing to comply with the written description requirement. Specifically, the Examiner has stated that "the claims encompass the attenuation of any gene in any vertebrate cell and the treatment of disease states in any vertebrate organism" and that "the specification provides insufficient written description to support the genus encompassed by the claims." More specifically, the Examiner stated that "a skilled artisan cannot envision the detailed structure of the encompassed genes and vertebrate cells." Applicants respectfully traverse the rejection.

The claims of the present invention are directed to methods for inhibiting the expression of a target gene using double stranded RNA. Applicant emphasizes that claims for the invention are directed to a *method.* Furthermore, the claims are not directed to particular genes or even particular double-stranded RNAs, as the method is suitable for use with any expressed gene in vertebrate cells. Applicant directs the Examiner to Example 10 in the Synopsis of Application of Written Description Guidelines, available at http://ww.uspto.gov/web/menu/written.pdf. The example is directed to what is necessary to satisfy the Written Description requirement for a biotechnology method claim involving binding to a particular gene. In example 10, it is noted that hybridization conditions described that will work for a species will support claims to a genus because of the stringency of the hybridization conditions. The independent claims of the present application both provide stringent hybridization conditions that strands of the dsRNA must satisfy, and thus should satisfy the written description requirement for the encompassed genes.

The written description requirement requires that a claimed genus may be satisfied through sufficient description of a representative number of species (MPEP 2163 IIA3(a)2).

Applicant has provided several example species representing diverse vertebrate classes (the zebrafish, chicken, and rat, described above) that support possession of a method of inhibiting gene expression in the genus of vertebrate cells. Furthermore, applicant has provided disclosure pertaining to the nature of the targeted gene in the section entitled "Targeted gene", running from page 10, line 7, to page 11, line 8, within the application. Genes for targeting can readily be selected by a researcher with a prior knowledge of a gene sequence. Alternatively, identification of particular genes that can be targeting for inhibition can be readily accomplished by "gene walking", or other methods that are used routinely by those skilled in the art. This procedure can be readily used to identify the nucleotide sequence of any expressed gene of interest, and once the nucleotide sequence of the target gene is known, it is equally routine to generate complementary RNA that can be used to inhibit expression of this gene. The complementarity of the RNA is defined by the claim as RNA strands that will hybridize to the target sequence under the conditions listed. As identification of gene sequences is routine in the art, it is respectfully submitted that the specification of the invention fully complies with the written description requirement.

The M.P.E.P, citing *Eli Lilly*, further indicates that satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the application was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed, and varies with the nature of the art. Applicant notes that the U.S. Patent No. 6,506,559 (issued to Fire et al., January 13, 2003) represents art of a similar nature to the present application, and that genus claims in this case were awarded on the basis of the disclosure of a single organism and experiments conducted primarily on the single unc-22 gene. As Applicant has far exceeded this standard, the present claims should satisfy the written description requirement.

It is accordingly submitted that the invention of claims 1-7, 9, 10, 15-25, 27-32, 39, 48, and 61-80 is adequately supported by the specification. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is, accordingly, requested.

The 35 U.S.C. §102 Rejection

The Examiner rejected claims 1-10, 15-26, 28-30, 62, 63, and 68-74 under 35 U.S.C. §102(e) as being anticipated by Fire et al (U.S. Patent 6,506,559). More specifically, the Examiner states that Fire et al. disclose a method of inhibiting gene expression *in vitro* by supplying a cell with a dsRNA. This rejection is respectfully traversed. However, Applicants have amended claim 1 and claim 63 to recite an in vivo method in vertebrates in the interest of furthering prosecution of the application.

For a reference to constitute an anticipatory reference, the prior art must contain an enabling disclosure. *Chester v. Miller*, 906 F.2d at 1576 n.2, 15 USPQ2d at 1336 n.2 (Fed. Cir. 1990). Applicant asserts that work done by Fire et al. in *C. elegans* does not provide an enabling disclosure for vertebrates, and in particular not for *in vivo* methods in vertebrates. Not only is *C. elegans* an invertebrate, but it is a primitive and simple invertebrate. It is only 1 mm long, includes only 959 somatic cells, and is often handled as a microorganism; for example, it is usually grown on petri plates seeded with bacteria. The description of dsRNA administration to this single, simple, invertebrate organism does not provide an enabling disclosure for in vivo methods in vertebrates claimed by Applicants.

Applicants thus respectfully submit that the teachings of the '559 patent are insufficient to anticipate the present invention, particularly in light of the amendments to the claims, and respectfully request that the rejection be withdrawn.

Summary

It is respectfully submitted that the pending claims 1-7, 9, 10, 15-25, 27-32, 39, 48, 62, 63, and 68-80 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

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CERTIFICATE UNDER 37 CFR §1.10:

"Express Mail" mailing label number: EV201891600 US Date of Deposit: 3-8-05
I hereby certify that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Sandy Truehart
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